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Synthesis and Liquid Crystal Properties of New Fluorinated Isoxazoles

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New fluorinated LC 3,5-diarylisoxazolines and 3,5-diarylisoxazoles have been synthesized and their thermal properties reported. Isoxazolines were synthesized using [3+2] 1,3-dipolar cycloaddition from nitrile oxide and alkenes with subsequent MnO_2-oxidation yielded the corresponding isoxazoles. The title compounds obtained were characterized by ^{1}H and ^{13}C NMR, differential scanning calorimetry (DSC), elemental analysis and polarized optical microscopy (POM). The final compounds are composed by terminal flexible hydrogenated alkyl chains or semiperfluoroalkyl chains. 3,5-diarylisoxazoline composed of alkyl chains is not LC, whereas when composed of one or two semiperfluoroalkyl chains it displays SmA mesophase. For 3,5-diarylisoxazoles a second mesophase SmC was also observed.

Keywords Isoxazolines; isoxazoles; fluorinated; [3+2] cycloaddition; MnO_2 oxidation.

Introduction

The incorporation of 5-membered heterocyclic rings, such as 1,3,4-oxadiazole, tetrazole, thiophene, isoxazoline, isoxazole and others, into molecular structures leads to considerable changes on molecular and mesomorphic properties [1]. In the world of 5-membered heterocyclic rings, isoxazoles are found in many natural and pharmaceutical products [2a–b]. Beyond well-known medicinal properties, isoxazolines and isoxazoles are interesting intermediates in organic synthesis [2c–d], and play an important role in the synthesis of novel liquid crystalline materials [2e–f]. The isoxazole ring incorporates a strong dipole moment and this polar effect favors the increasing of molecular anisotropic polarizability. Consequently, it induces the formation of stable mesophase with enantiotropic behavior [3]. The special features concerning the chemical nature of isoxazoles can be greatly improved with the installation of fluorine atoms at peripheral region of diarylisoxazoles represented by semiperfluoroalkyl chains or connected directly into the aryl groups. The combination of different characteristics, as small size, high polarity, great stability (due to the high strength of the C—F bond) and low polarizability has stimulated the study of fluorine influence on the control of the liquid crystalline properties. The important attributes of the fluorine

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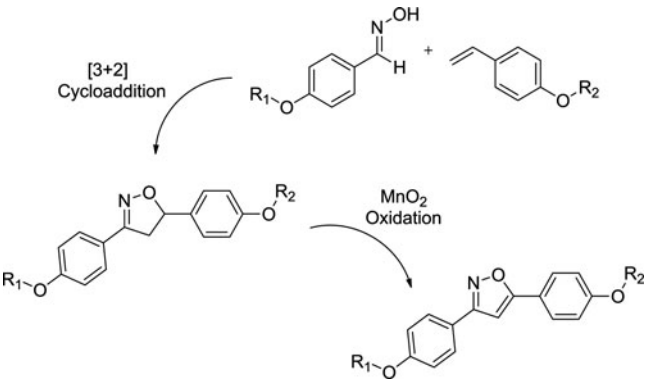


Figure 1. Synthesis of isoxazolines by [3+2] 1,3-dipolar cycloaddition followed by MnO_2-oxidation reaction.

substituent ensure that significant modifications are frequently encountered in respect of melting point, mesophase morphology and transition temperatures [4].

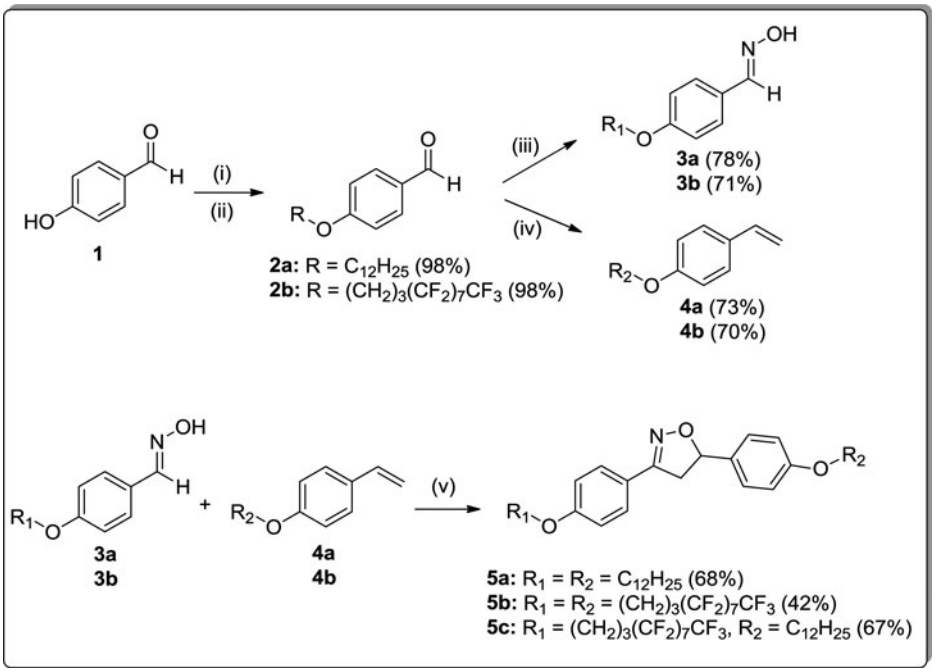
Herein we are describing the synthesis and characterization of new liquid crystals based on fluorinated isoxazoles. Isoxazoles were obtained in two steps transformation - [3+2] 1,3-dipolar cycloaddition of nitrile oxide with alkene to access the key intermediate isoxazolines. MnO_2-oxidation reaction of isoxazolines renders the corresponding isoxazoles. This synthetic methodology has been largely used by us in the preparation of new LC materials [5] and its main attribute is the high regioselectivity in favor of 3,5-disubstituted isoxazolines [6].

In the strategy depicted briefly in Figure 1, the oxime is the precursor for the active nitrile oxide which acts as 1,3-dipolar component for cycloaddition and alkene is the dipolarophile for [3+2] 1,3-dipolar cycloaddition. The key intermediate 3,5-diarylisoxazoline is subsequently oxidized using MnO_2 to reach the final isoxazole [5].

Results

Classical synthetic methodologies were employed in the preparation of the oximes and alkenes, as we can see in the Scheme 1. The synthetic route started from 4-hydroxybenzaldehyde (**1**), which was alkylated [7] to obtain the compounds **2a** and **2b**, Aldehydes **2a** and **2b** were precursors for the oximes **3a** and **3b** as well as the alkenes **4a** and **4b**. Aldehydes **2a** and **2b** were composed of terminal segments of flexible alkyl chain (hydrogenated chain) and semiperfluoroalkyl chain, respectively. Wittig olefination was employed to synthesize the alkenes **4a-b** [8], and the oximes **3a-b** were obtained by a well-established procedure in the literature [9]. It is important to highlight that alkenes and oximes are originated from the same chemical precursors. With the appropriate alkenes and oximes synthesized in good yields, the [3+2] 1,3-dipolar cycloadditions were carried out using a 5% aqueous NaOCl solution as oxidizing agent, to form the 3,5-disubstituted isoxazolines in high regioselectivity.

To accomplish the final synthesis of title compounds, the oxidation step using activated MnO_2, that present low toxicity, low cost, ease of handling and the absence of hazardous additives/byproducts [10], led to the isoxazoles **6a**, **6b** and **6c** in 55%, 43% and 67% yields, respectively, as outlined in the Figure 2.



Scheme 1. Synthetic routes to obtain the alkenes, oximes and isoxazolines (i) to form product **2a**: *n*-dodecyl bromide, K_2CO_3, TBAB, butanone, reflux, 18h; (ii) to form product **2b**: 3-(perfluorooctyl)propyl iodide, K_2CO_3, DMF, 60°C, 18h; (iii) $NH_2OH.HCl$, EtOH, NaOAc, H_2O, reflux, 1h; (iv) methyltriphenylphosphonium bromide, NaH, THF, room temperature, 24h; (v) NaOCl 5%, CH_2Cl_2, 30 min.

The chemical structures of all final compounds synthesized were characterized by ^1H and ^{13}C NMR and elemental analysis. Thermal and liquid crystalline properties were investigated by POM and DSC. LC samples were first filtered from DCM solution to remove dusty, paper fibers, etc and after analyzed by POM and DSC. The transitional properties are tabulated in Table 1. As we can see, the isoxazolines containing semiperfluoroalkyl chains displayed liquid-crystalline behavior. The compound **5a** only showed the existence of two different crystalline forms, while the isoxazoline **5b** with two semiperfluoroalkyl chains showed monotropic SmA mesophase. Isoxazoline **5c**, having two mixed flexible segments formed by hydrogenated alkyl chain and semiperfluoroalkyl chain, presented enantiotropic SmA mesophase with a greater transition temperature range than **5b**. Here we can see a

Figure 2. Oxidation reaction used to synthesize the isoxazoles **6a**, **6b** and **6c**.

Table 1. Transition temperatures (°C) and enthalpy values (kJ/mol) for the isoxazolines **5a-c** and isoxazoles **6a-c**

LC	Transition temperatures (°C)	ΔH (kJ/mol)
5a	Cr_1 102.3 Cr_2 105.1 I	Cr_1 49.8 Cr_2 38.1 I
5b	I (150.7) SmA* 136.2 Cr	I (2.5) SmA* 43.1 Cr
5c	Cr 111.6 SmA 135.7 I	Cr 28.0 SmA 5.4 I
6a	Cr 104.0 SmC 148.9 I	Cr 65.7 SmC 8.8 I
6b	Cr 186.8 SmC 203.2 SmA 213.1 I	Cr 42.7 SmC 3.3 SmA 1.7 I
6c	Cr 116.0 SmC 172.9 SmA 199.3 I	Cr 31.0 SmC 0.8 SmA 6.7 I

Cr, Cr_1 and Cr_2 = Crystal phases; SmA = Smectic A phase; SmC = Smectic C phase; I = Isotropic phase; *Monotropic behavior.

clear effect of segregation exerted by fluorine atoms presented in the carbon backbone. All the isoxazoles **6a-c** displayed the existence of liquid crystalline properties, exhibiting enantiotropic mesophases. For compound **6a** a SmC was observed as previously reported in the literature [11]. The new isoxazoles **6b** and **6c** displayed two smectic mesophases. Upon cooling from isotropic state, samples **6b** and **6c** entered to SmA phase followed by a second transition to the SmC mesophase as evidenced clearly by the textures observed using POM analysis. DSC curves of those samples also corroborated for the assignment of this second transition between mesophases. Mesophase range and enthalpy values for **5b-c** and **6a-c** are definitely a manifestation of influence of fluorine atom on transition properties of the compounds reported here [4c, 12, 13]. Incompatibility of totally flexible alkyl chain, rigid anisometric core and less flexible semiperfluorinated alkyl chain are responsible for the formation of positional ordered liquid-crystalline phases [14] as observed in Table 1.

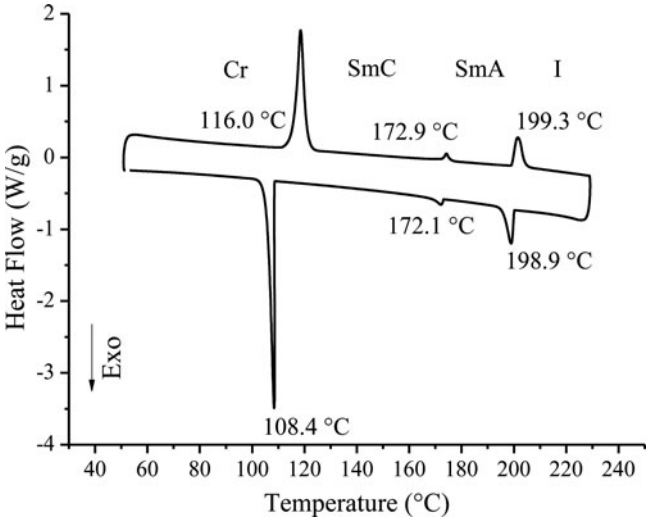


Figure 3. DSC curve for the LC compound **6c** upon second heating and cooling at a rate of 10 °Cmin^{-1}.

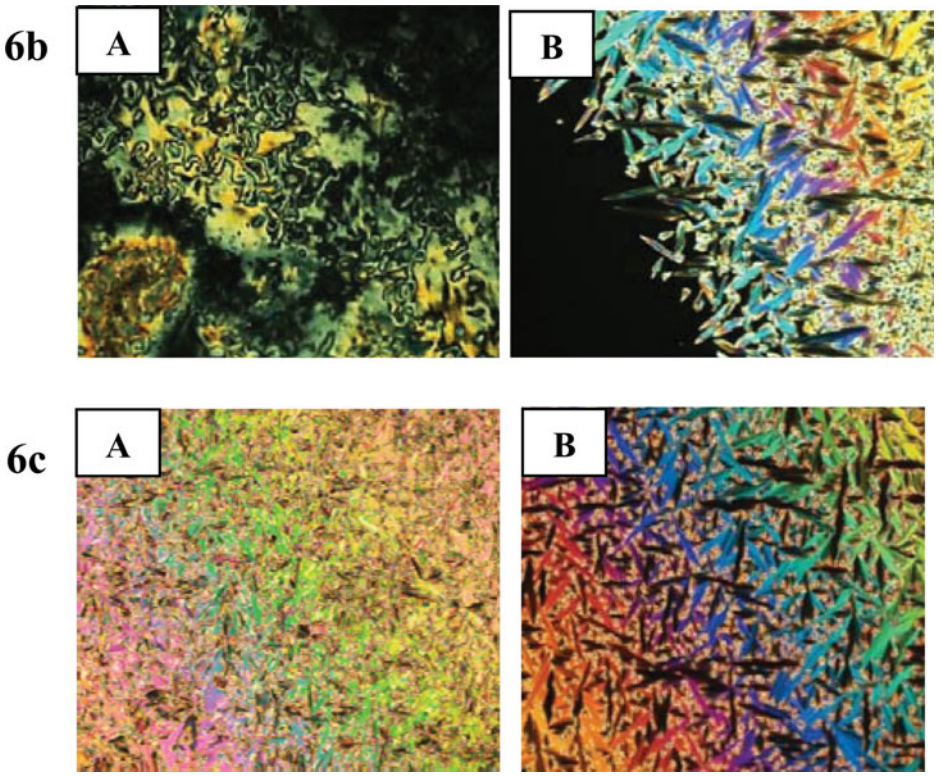


Figure 4. Optical textures observed in the mesophases A) SmC and B) SmA obtained upon cooling from isotropic phase of the isoxazoles **6b** and **6c**.

In the Figure 3 the DSC curve for the isoxazole **6c** is shown, where it is possible to observe the peaks associated to the phase transitions. Considering the enantiotropic behavior of the samples in this study, there are three peaks upon heating (the sample passes from crystal phase to smectic C phase, then to smectic A phase, and finally reaches the isotropic phase). Upon cooling, sample **6c** enters to SmA mesophase at 198.9°C from isotropic state and at 172.1°C a second transition to SmC is seen. At 108.4°C the crystallization of sample **6c** from SmC mesophase to crystal phase occurs.

All mesophases were identified according to their textures observed by optical microscopy (see Figure 4). Once the isotropic liquid is cooled, a focal-conic texture appears in the smectic A phase for the compounds **6b** and **6c**. Cooling down, a *Schlieren* and a broken focal-conic textures allow us to identify smectic C phase for the LC **6b** and **6c**, respectively.

Conclusion

We have synthesized new 3,5-diarylisoxazolines and 3,5-diarylisoxazoles **5a-c** and **6a-c**, respectively using an efficient and regioselective synthetic route. **5a** and **6a** are composed by terminal flexible hydrogenated alkyl chain in both sides of the rigid core. **5b** and **6b** have terminal flexible semiperfluoroalkyl chains in both sides and **5c** and **6c** are composed by terminal flexible alkyl chains from one side and to the other side by terminal segments of

semiperfluoroalkyl chains. Isoxazoline **5a** did not show liquid crystalline behavior, whereas isoxazole **6a** showed only mesophase SmC. The isoxazolines **5b** and **5c** presented SmA mesophases, monotropic and enantiotropic, respectively. Conversion to more anisotropic isoxazoles **6b** and **6c** stable mesophases arose. By comparison with the isoxazole **6a** that presented mesophase SmC, the incorporation of fluorine atoms modified the thermal behavior, favoring also the formation of SmA mesophase for the compounds **6b** and **6c**. Calamitic isoxazole **6c**, that has only one side with polyfluorinated chain, showed the lowest transition temperatures and the greatest mesophase range. Improved mesophase range of the **6c** compared to the isoxazoles **6b** with two polyfluorinated chains is a clearly segregation effect induced by the two different flexible chains in their polar character. The combination of better conjugation of isoxazole ring and polar effect of semiperfluorinated alkyl chain induce the formation of structured layer mesophase by means of segregation effect. As expected, fluorinated alkyl chain induced the formation of orthogonal mesophase by means of segregation effect. Therefore, this research contributed to a better understanding of the structure-property relationship in molecules such as 3,5-disubstituted isoxazoles containing long fluorinated chains and facilitates the design of new and more complex compounds.

Experimental

General

The melting point and textures of the samples were determined using an Olympus BX 41 polarizing microscope in conjunction with a Mettler Toledo FP-90 controller and HT84 heating stage. The transition temperatures and enthalpies were determined using a TA Instruments DSC Q20 differential scanning calorimeter, the heating and cooling rate was 10 $^{\circ}$Cmin^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded at Varian 300 MHz and Bruker Avance 400 MHz instruments. Chemical shifts are given in parts per million (δ) and they are referenced to tetramethylsilane (TMS).

Alkylation Reactions

The products **2a** and **2b** were prepared from 4-hydroxybenzaldehyde (**1**) following previously reported procedures [7].

Synthesis of Aldoximes

The oximes **3a** and **3b** were synthesized from the corresponding benzaldehyde by treatment with a hydroxylamine hydrochloride solution according to literature procedures [9].

Synthesis of Alkenes

To prepare the alkenes **4a** and **4b** the Wittig reaction was used according to the procedure described in the reference [8].

Procedure for the 1,3-dipolar Cycloaddition Reactions

To a solution of alkene (1.0 mmol) and oxime (1.0 mmol) in dichloromethane (4 mL) at room temperature, was added dropwise a 5% aqueous sodium hypochlorite solution

(3.0 mL, 2.0 mmol). After the completed addition, the reaction mixture was stirred for 30 min. The CH_2Cl_2 was evaporated in vacuum and water was added to the reaction mixture to filter and wash the product. Isoxazolines **5a-c** were recrystallized from ethanol and filtered off and dried.

3,5-bis[4-(dodecyloxy)phenyl]isoxazoline (5a): White solid; Yield: 68%; mp Cr_1 102.3°C Cr_2 105.1°C I; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.64$ (m, 2H), 7.32 (m, 2H), 6.92 (m, 4H), 5.67 (dd, 1H, $J_{cis} = 10.7$ Hz, $J_{trans} = 8.6$ Hz), 3.98 (m, 4H), 3.72 (dd, 1H, $J_{gem} = 16.5$ Hz, $J_{cis} = 10.8$ Hz), 3.32 (dd, 1H, $J_{gem} = 16.5$ Hz, $J_{trans} = 8.6$ Hz), 1.80 (m, 4H), 1.46 (m, 4H), 1.30 (m, 32H), 0.90 (t, 6H, $J = 6.7$ Hz); ^{13}C NMR (101 MHz, $CDCl_3$) $\delta =$ 160.7, 159.1, 155.9, 132.7, 128.2, 127.4, 121.9, 114.7, 82.2, 68.1, 68.1, 43.2, 31.9, 29.7, 29.7, 29.6, 29.6, 29.4, 29.4, 29.4, 29.3, 29.2, 26.0, 26.0, 22.7, 14.1; $C_{39}H_{61}NO_3$: calcd. C 79.14, H 10.39, N 2.37; found C 79.27, H 10.69, N 2.33.

3,5-bis[4-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyloxy)phenyl]isoxazoline (5b): White solid; Yield: 42%; Transition temperatures: I (150.7°C) SmA 136.2°C Cr; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.66$ (m, 2H), 7.35 (m, 2H), 6.94 (m, 4H), 5.69 (dd, 1H, $J_{cis} = 10.7$ Hz, $J_{trans} = 8.5$ Hz), 4.11 (t, 2H, $J = 5.9$ Hz), 4.07 (t, 2H, $J = 5.9$ Hz), 3.73 (dd, 1H, $J_{gem} = 16.5$ Hz, $J_{cis} = 10.8$ Hz), 3.31 (dd, 1H, $J_{gem} = 16.5$ Hz, $J_{trans} = 8.5$ Hz), 2.34 (m, 4H), 2.14 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 160.0$, 158.6, 155.6, 133.4, 128.2, 127.3, 122.6, 114.7, 114.7, 82.1, 66.5, 43.1, 28.0 (t, CH_2-CF_2, $J = 22.3$ Hz), 20.6; $C_{37}H_{23}F_{34}NO_3$: calcd. C 37.80, H 1.97, N 1.19; found C 37.97, H 2.09, N 1.20.

5-[4-(dodecyloxy)phenyl]-3-[4-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyloxy)phenyl]isoxazoline (5c): White solid; Yield: 67%; Transition temperatures: Cr 111.6°C SmA 135.7°C I; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.63$ (m, 2H), 7.30 (m, 2H), 6.90 (m, 4H), 5.65 (dd, 1H, $J_{cis} = 10.7$ Hz, $J_{trans} = 8.6$ Hz), 4.07 (t, 2H, $J =$ 5.8 Hz), 3.94 (t, 2H, $J = 6.6$ Hz), 3.69 (dd, 1H, $J_{gem} = 16.6$ Hz, $J_{cis} = 10.8$ Hz), 3.29 (dd, 1H, $J_{gem} = 16.6$ Hz, $J_{trans} = 8.6$ Hz), 2.33 (m, 2H), 2.13 (m, 2H), 1.77 (m, 2H), 1.42 (m, 2H), 1.28 (m, 16H), 0.88 (t, 3H, $J = 6.7$ Hz); ^{13}C NMR (101 MHz, $CDCl_3$) $\delta = 160.0$, 159.2, 155.7, 132.6, 128.3, 127.4, 122.6, 114.7, 114.6, 82.3, 68.1, 66.4, 43.1, 31.9, 29.7, 29.6, 29.6, 29.6, 29.4, 29.4, 29.2, 27.9 (t, CH_2-CF_2, $J = 22.4$ Hz), 26.0, 22.7, 20.5, 14.1; $C_{38}H_{42}F_{17}NO_3$: calcd. C 51.65, H 4.79, N 1.58; found C 51.82, H 4.96, N 1.55.

Procedure for the Oxidation Reactions

To a flask adapted with a Dean-Stark were added 3,5-disubstituted isoxazoline (1.0 mmol), toluene (35 ml) and MnO_2 (18.0 mmol). The mixture was heated under reflux. Reactions were monitored by thin-layer chromatography. After observing that all the isoxazoline was consumed, it was filtered over celite, washed with CH_2Cl_2 and concentrated in vacuum to give the solid which were purified by recrystallization in ethanol.

3,5-bis[4-(dodecyloxy)phenyl]isoxazole (6a): White solid; Yield: 55%; Transition temperatures: Cr 104.0°C SmC 148.9°C I; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.76$ (m, 4H), 6.97 (m, 4H), 6.63 (s, 1H), 4.01 (t, 4H, $J = 6.5$ Hz), 1.81 (m, 4H), 1.45 (m, 4H), 1.27 (m, 32H), 0.88 (t, 6H, $J = 6.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 170.2$, 162.5, 160.7, 160.6, 128.1, 127.3, 121.7, 120.3, 114.9, 114.8, 95.8, 68.2, 68.2, 31.9, 29.6, 29.6, 29.5, 29.5, 29.3, 29.3, 29.3, 29.2, 29.2, 26.0, 26.0, 22.6, 14.0; $C_{39}H_{59}NO_3$: calcd. C 79.41, H 10.08, N 2.37; found C 79.86, H 10.77, N 2.46.

3,5-bis[4-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyloxy)phenyl]isoxazole (6b): White solid; Yield: 43%; Transition temperatures: Cr 186.8°C SmC 203.2°C SmA 213.1°C I; ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 120°C) $\delta = 7.80$ (t, 4H, $J =$

8.2 Hz), 7.04 (d, 4H, $J = 8.3$ Hz), 6.64 (s, 1H), 4.17 (t, 4H, $J = 5.5$ Hz), 2.39 (m, 4H), 2.18 (m, 4H).

5-[4-(dodecyloxy)phenyl]-3-[4-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyloxy)phenyl]isoxazole (6c): White solid; Yield: 67%; Transition temperatures: Cr 116.0°C SmC 172.9°C SmA 199.3°C I; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.82$ (d, 2H, $J = 8.6$ Hz), 7.77 (d, 2H, $J = 8.6$ Hz), 7.01 (d, 4H, $J = 8.0$ Hz), 6.67 (s, 1H), 4.12 (t, 2H, $J = 5.7$ Hz), 4.03 (t, 2H, $J = 6.4$ Hz), 2.34 (m, 2H), 2.16 (m, 2H), 1.82 (m, 2H), 1.49 (m, 2H), 1.29 (m, 16H), 0.90 (t, 3H, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta =$ 170.3, 162.4, 160.7, 159.9, 128.2, 127.3, 122.4, 120.2, 114.9, 114.8, 95.7, 68.2, 66.4, 31.9, 29.6, 29.5, 29.3, 29.3, 29.3, 29.1, 28.0 (t, CH_2-CF_2, $J = 22.5$ Hz), 25.9, 22.6, 20.6, 13.9; $C_{38}H_{40}F_{17}NO_3$: calcd. C 51.76, H 4.57, N 1.59; found C 51.48, H 4.49, N 1.51.

Acknowledgments

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